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Mini-review

Hepatic iron overload and hepatocellular carcinoma

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ABSTRACT

The liver is the main storage site for iron in the body. Excess accumulation of iron in the liver has been well-documented in two human diseases, hereditary hemochromatosis and dietary iron overload in the African. Hepatic iron overload in these conditions often results in fibrosis and cirrhosis and may be complicated by the development of hepatocellular carcinoma. Malignant transformation usually occurs in the presence of cirrhosis, suggesting that free iron-induced chronic necroinflammatory hepatic disease plays a role in the hepatocarcinogenesis. However, the supervention of hepatocellular carcinoma in the absence of cirrhosis raises the possibility that ionic iron may also be directly hepatocarcinogenic. Support for this possibility is provided by a recently described animal model of dietary iron overload in which iron-free preneoplastic nodules and hepatocellular carcinoma developed in the absence of fibrosis or cirrhosis. The mechanisms by which iron induces malignant transformation have yet to be fully characterized but the most important appears to be the generation of oxidative stress. Free iron generates reactive oxygen intermediates that disrupt the redox balance of the cells and cause chronic oxidative stress. Oxidative stress leads to lipid peroxidation of unsaturated fatty acids in membranes of cells and organelles. Cytotoxic by-products of lipid peroxidation, such as malondialdehyde and 4-hydroxy-2′-nonenal, are produced and these impair cellular function and protein synthesis and damage DNA. Deoxyguanosine residues in DNA are also hydroxylated by reactive oxygen intermediates to form 8-hydroxy-2′-deoxyguanosine, a major promutagenic adduct that causes G:C to T:A transversions and DNA unwinding and strand breaks. Free iron also induces immunologic abnormalities that may decrease immune surveillance for malignant transformation.

1. Introduction

Iron in its free ferrous or ferric states is ubiquitous in cells and is essential for their normal functioning. But in excess amounts free iron is toxic to cells. Hepatocytes are the main storage site of iron in the body, and under normal conditions these cells are capable of safely storing the transition metal as ferric oxyhydroxyapatite in the core of the ferritin protein. However, at a critical level of iron overload the capacity for safe sequestration is exceeded and denaturation of the protein subunits occurs, releasing ionic iron into the cytoplasm of the hepatocytes. Accordingly, the liver is the organ most likely to be afflicted by iron overloading. The consequences of hepatic iron overload have most fully been documented in patients with hereditary hemochromatosis (HH), a not uncommon genetic disorder in individuals of Celtic descent, and in Africans with dietary iron overload (previously called Bantu visceral siderosis). Its detrimental effects on the liver in other iron storage conditions, such as thalassemia major, sideroblastic anemias, and spherocytosis, have received less attention.

Excess accumulation of iron in the liver of patients with HH is almost invariably complicated by hepatic fibrosis and cirrhosis [1]. Moreover, hepatocellular

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carcinoma (HCC) often supervenes, almost always in a cirrhotic liver, and the longer the patient survives the more likely is this sequence of events to occur [2,3]. Hepatic fibrosis and cirrhosis also complicate abnormal hepatic iron storage in patients with African dietary iron overload, although both, but cirrhosis in particular, do so appreciably less often than they do in HH [4–6]. HCC was initially thought not to occur in dietary iron overload [7–9]. However, during recent years an increased risk for this complication has been documented in three case/control studies [10–12], and an animal model for dietary iron overload as a cause of HCC has been reported [13,14].

Excess hepatic iron accumulation as a cause of HCC is the subject of this review.

2. Hereditary hemochromatosis and hepatocellular carcinoma

HCC has long been known to occur in patients with HH, is one of its major complications, and is the most frequent cause of premature death [2,15,16]. The mortality rate from HCC in this condition has been estimated to be 8% [17], with age-adjusted relative risk rates for developing the tumor ranging between 93 and over 200 per 100,000 of the population per annum [1,3,15]. Cirrhosis is present in almost all of the patients who develop HCC. The prevalence of tumor formation in these patients is appreciably higher (18.5%) than that in those with HH in general (10.7%) [16]. So close is the association between the presence of cirrhosis and the supervention of HCC that the view has generally been held that chronic hepatic necroinflammatory disease rather than excess hepatic iron *per se* was responsible for the malignant transformation. This view was reinforced by the observations that long-term survival in HH patients in whom cirrhosis was prevented by repeated phlebotomy was not worse than that in the general population [2,18] and that the risk of HCC formation in HH patients with cirrhosis remained even after they had been de-ironed [19]. Cirrhosis, whatever its cause, is known to be complicated by HCC [20]. Early comparisons between the incidence of HCC in HH and in other causes of cirrhosis showed the risks to be similar [21,22], an observation compatible with the belief that cirrhosis played a pivotal role in hepatocarcinogenesis in patients with HH.

But HCC does occur, although rarely, in HH patients without cirrhosis [23–28], suggesting that hepatic iron storage *per se* might be directly hepatocarcinogenic in addition to its indirect effect through the supervention of cirrhosis. A recent comparison between the incidence of cirrhosis in HH and that in other diseases revealed a higher risk of HCC development in the former [29], in keeping with an added direct hepatocarcinogenic effect of hepatic iron accumulation. This view was also supported by reports of HCC in patients with African dietary iron overload [10–12] and of the development of iron-free preneoplastic nodules and HCC in the absence of fibrosis and cirrhosis in an animal model of dietary iron overload [13,14].

3. Dietary iron overload in the African

African dietary iron overload was first described by Strachan in 1929 in Blacks from southern and central Africa [30]. It later became evident that this condition occurs in several countries in sub-Saharan Africa, where it may affect as many as 15% of Black adult males [4–6,31,32]. African dietary iron overload occurs predominantly in rural areas [6,32–34], where 80% of the Black population in sub-Saharan Africa lives and where more than two-thirds of adult males consume home-brewed beer. Hepatic iron concentrations comparable with those in HH result from the consumption over time of large volumes of this traditional beer. The beer has a high iron content (46–82 mg/L compared with <0.5 mg/L in commercial beers) that results from the beverage being prepared in cast iron drums or containers [4,6,34]. During the fermentation of sorghum or other locally-grown crops the pH of the ferment decreases to very low levels (3.7 or 3.8), leaching iron from the container into the contents [35]. This iron is in an ionized, highly bioavailable form [35]. The more severe degrees of accumulated hepatic iron may be complicated by portal fibrosis or, less often, cirrhosis [36,37]. Histological features of alcoholic liver disease are rarely evident (the alcohol content of the beer is only approximately 3%) and the amounts of iron present far exceed those that may occur in alcohol-induced liver disease [4–6,34,38]. Unlike HH, in which iron overload occurs predominantly in hepatocytes [39,40], iron accumulation in dietary iron overload affects both macrophages and hepatocytes [40,41].

Because only some African Blacks consuming large volumes of the iron-rich beer develop hepatic iron overload, and because the condition does not occur in other parts of the world, it has been suggested that genetic predisposition may play a role in the pathogenesis of dietary iron overload [42]. However, a putative gene has not yet been identified.

Three case/control studies during recent years have documented a causal association between African dietary iron overload and HCC [10–12]. In a re-analysis of the pathological material that formed the basis of Strachan's thesis, Gordeuk et al. calculated a relative risk of HCC development of 23.5 (95% confidence limits 2.1 and 225) in those subjects with the highest levels of hepatic iron accumulation, after allowing for the confounding effect of cirrhosis [10]. Shortly thereafter, Moyo et al. reported a relative risk of HCC of 3.1 (95% confidence limits 1.05 and 9.4) in Zimbabwean Blacks with dietary iron overload, after adjusting for the confounding effects of cirrhosis [11]. The major environmental risk factors for HCC in African Blacks are chronic hepatitis B virus infection and prolonged dietary exposure to the fungal toxin, aflatoxin B_1. In neither of these studies were other risk factors included in the analysis. Mandishona et al. reported a relative risk of HCC of 10.6 (95% confidence limits 1.5 and 76.8) and a population attributable risk of 29 in rural South African Blacks, after adjusting for the confounding effects of these other risk factors as well as the lesser risk factor in this population, chronic hepatitis C virus infection [12]. The possible aetio-